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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,209	10/16/2006	Samuel Waksal	13821/48902	2944
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KENYON & KENYON LLP ONE BROADWAY NEW YORK, NY 10004			EXAMINER AEDER, SEAN E	
			ART UNIT	PAPER NUMBER
			1642	
			NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspto@kenyon.com

Office Action Summary

Application No.

10/560,209

Applicant(s)

WAKSAL, SAMUEL

Examiner

Sean E. Aeder

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 September 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 3-7, 10 and 12-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 8, 9 and 11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 12/9/05
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application
- ☐ Other: _____

Detailed Action

Election/Restriction

The response filed on 9/7/07 to the restriction requirement of 4/4/07 has been received. Applicant has elected, without traverse, Group III and the following species: "ABX-EGF" and "OSI-774".

Due to an overlap in subject matter, claim 2 has been incorporated into all groups linked by claim 1 (groups I-IV). Further, due to the fact that the pending claims recite only one species of the elected group (bevacizumab) and that the elected species are encompassed by unelected inventions, the species "bevacizumab" is rejoined.

Claims 1-21 are pending.

Claims 3-7, 10, and 12-21 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 1, 2, 8, 9, and 11 are currently under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 9 are rejected because claim 8 recites: "The method of claim 1 or 2, wherein the RTK...". Since claim 1 makes reference to more than one RTK (the RTK to be inhibited, the RTK of which an extracellular antagonist is to be administered, and the RTK of which an intracellular antagonist is to be administered), there is insufficient antecedent basis for "the RTK" as recited in claim 8.

Claim 9 is rejected for reciting: "...wherein the extracellular RTK antagonist is bevacizumab". Paragraph 35 indicates that bevacizumab is related to Avastintm; however, it is unclear if, or how, the formulation of bevacizumab differs from Avastintm. Amending claim 9 to recite "...wherein the extracellular RTK antagonist is AvastinTM ~~bevacizumab~~" would obviate this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 8, 9, and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of (1) a genus of extracellular RTK antagonists and (2) a genus of intracellular RTK antagonists. The written description in this case sets forth antibodies that

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specifically bind VEGFR as examples of extracellular VEGFR antagonists (see paragraphs 34-35, in particular). Further, the specification lists AXD-6474, CEP-5214, and ZD-6474 as examples of intracellular VEGFR antagonists (see paragraph 45, in particular). The specification does not disclose, and the prior art does not teach, the broad genera of antagonists encompassed by the claims.

The specification discloses that extracellular RTK antagonists interact with the extracellular binding region of the RTK such that tyrosine kinase activity is inhibited (see paragraph 18, in particular). The specification further discloses that intracellular RTK antagonists inhibit tyrosine kinase activity of the RTK by preventing receptor phosphorylation and/or the phosphorylation of other proteins involved in the various RTK signaling pathways (see paragraph 19, in particular). The specification further discloses that the extracellular and intracellular antagonists *broadly* encompass biological molecules, small molecules, or any other substance that inhibits activation of an RTK by interaction with the extracellular binding region of the receptor (extracellular antagonist) or inhibits phosphorylation by interaction with the intracellular tyrosine kinase domain or *any* other protein involved in the pathway (intracellular antagonist) (see paragraph 22, in particular).

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to that genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be

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achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Further, in regards to a method utilizing a product defined by function, without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. See *Eli Lilly*, 119 at 1568 USPQ2d at 1406 ("definition by function...does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is").

The inventions at issue in *Lilly* were DNA constructs per se, the holdings of that case is also applicable to claims such as those at issue here. Further, disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

The court has since clarified that this standard applies to compounds other than cDNAs. See *University of Rochester v. G.D. Searle & Co., Inc.*, F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genera. That is, the specification provides neither a representative number of antagonists that encompass the genera nor does it provide a description of structural features that are common to the genera. Since the disclosure fails to describe common attributes or characteristics that identify members of the genera, and because

the genera are highly variant, the disclosure insufficiently describes the genera. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genera as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genera, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Applicant is reminded that *Vas-Cath* makes clear

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that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1, 2, 8, 9, and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting a particular receptor tyrosine kinase comprising administering products that act as extracellular and intracellular antagonists for said particular receptor tyrosine kinase, the specification does not reasonably provide enablement for methods of inhibiting just any receptor tyrosine kinase comprising administering extracellular and intracellular antagonists of just any receptor tyrosine kinase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are broadly drawn to methods of inhibiting just any receptor tyrosine kinase comprising administering extracellular and intracellular antagonists of just any receptor tyrosine kinase. This includes methods of inhibiting VEGFR by

administering products that do not antagonize VEGFR (such as the elected species ABX-EGF and OSI-774). The elected species ABX-EGF and OSI-774 specifically antagonize receptor tyrosine kinases other than VEGFR (see paragraph 30 of the specification, in particular).

The specification discloses lists of products that would specifically antagonize one receptor tyrosine kinase, but would not specifically antagonize another receptor tyrosine kinase. For instance, bevacizumab (AVASTIN[™]) is a monoclonal antibody disclosed by the specification to be a "specific" VEGFR antagonist (see paragraph 35 and claim 9) and is taught in the art by Rosen (Cancer Control, Mar-Apr 2002, 9(2) (supplement): 36-44) to specifically bind and antagonize VEGFR (see page 41, in particular). Due to the guidance of the disclosure and the teachings of Rosen, one of skill in the art would recognize that monoclonal antibodies that specifically bind VEGFR would *not* predictably interact with, antagonize, or inhibit the activity of any or every other receptor tyrosine kinase.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to methods of inhibiting just any receptor tyrosine kinase comprising administering extracellular and intracellular antagonists of just any receptor tyrosine kinase, and Applicant has not enabled said method because the specification provides guidance against said method, the art teaches against said method, and it has not been shown that just any receptor tyrosine kinase antagonist would predictably inhibit every receptor tyrosine kinase.

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In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 8, and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Alitalo et al (US 2002/0164667 A1; 11/7/02), as evidenced by Fong et al (Cancer Research, 1/1/99, 59:99-106).

The claims are drawn to a method of inhibiting an RTK in a mammal comprising administering an extracellular RTK antagonist and an intracellular RTK antagonist. As evidenced by Fong et al, SU5416 is an intracellular VEGFR antagonist (see right column of page 99, in particular).

Alitalo et al teaches a method of treating tumor growth or angiogenesis in a mammal by inhibiting VEGFR in a mammal comprising administering an extracellular VEGFR antagonist, such as an anti-VEGFR antibody and/or a peptide that functions as an extracellular VEGFR antagonist by inhibiting VEGF from binding VEGFR, and an

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intracellular VEGFR antagonist, such as SU5416, to the mammal (see paragraphs 60, 75, 135, 208, in particular). Alitalo et al teaches a method further comprising administering an antineoplastic agent (see paragraph 62, in particular).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, 8, 9, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alitalo et al (US 2002/0164667 A1; 11/7/02) as applied to claims 1, 2, 8, and 11 above, and further in view of Rosen (Cancer Control, Mar-Apr 2002, 9(2) (supplement): 36-44).

The teaching of claims 1, 2, 8, and 11 by Alitalo is discussed above. Alitalo et al does not specifically teach a method comprising administering the extracellular VEGFR antagonist bevacizumab (claim 9). However, this deficiency is made up in the teachings of Rosen.

Rosen teaches a method of treating tumor growth or angiogenesis by administering bevacizumab, an anti-VEGFR monoclonal antibody produced by Genentech (San Francisco, CA) (right column of page 41, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to perform the method of treating tumor growth or angiogenesis in a

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mammal by inhibiting VEGFR in a mammal taught by Alitalo et al with the extracellular VEGFR antagonist bevacizumab because Alitalo et al teaches performing said method with an anti-VEGFR antibody produced by Genentech (San Francisco, CA) (see paragraph 208, in particular) and Rosen teaches bevacizumab is an anti-VEGFR antibody produced by Genentech (San Francisco, CA) that is used to treat tumor growth or angiogenesis (right column of page 41, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for performing the method of treating tumor growth or angiogenesis in a mammal by inhibiting VEGFR in a mammal taught by Alitalo et al with the extracellular VEGFR antagonist bevacizumab because Alitalo et al teaches performing said method with an anti-VEGFR antibody produced by Genentech (San Francisco, CA) (see paragraph 208, in particular) and Rosen teaches bevacizumab is an anti-VEGFR antibody produced by Genentech (San Francisco, CA). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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